REMARKS/ARGUMENTS

Prior to submission of this amendment, claims 31, 35-38, 40-47, 51-52 and 56-57, 59-61 were pending. Claims 31, 40, 56, 57 and 60 have been amended to recite that the EGFR receptor is ErbB1. One skilled in the art would know that the EGFR receptor is also referred to as ErbB1. Support for this is found in the attached dictionary of Cancer Terms from the National Cancer Institute which indicates that ErbB1 is also called EGFR. Claim 31 has been amended to recite the scientific name of LAMC2 and GPC3. Support for this amendment can be found in the NCBI printouts for each gene (enclosed herewith).

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications. No new matter is added by this amendment.

Interview

Applicants thank the Examiner for the courtesies extended during the interview on April 25, 2007. At the interview, the rejection of the claims under 35 U.S.C. 112, first and second paragraph were discussed and suggestions were made regarding ways to amend the claims to overcome the enablement rejection. At the interview, applicants were asked to insert the name of LAMC2 and GPC3 into the first claim.

Election/Restriction

The Examiner indicated that with respect to the further restriction requirement with respect to the additional genes listed in Claim 60, the restriction is maintained. In reply, Applicants again note that this claim depends from claim 31 and requires determining the expression level of additional RNA transcripts or products. Clearly if claim 31 is allowable, then claim 60 is allowable. There is not an undue burden on the examiner for searching purposes.

Applicant had elected CD44v6.

Rejection under 35 U.S.C. 112, first paragraph (enablement)

Claims 31, 35-39, 41-47, 51-52, 56-61 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claims allegedly contain

subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (page 3-4). The Office Action states that the specification does not provide enablement for methods for determining the normalized level of LAMC2 or GPC3 in a sample and determining the normalized level of the corresponding gene products of LAMC2 or GPC3 in a sample.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation [1] [2]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue [4] [5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors (i.e., the In re Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[6] [7]. "Limitations and examples in the specification do not generally limit what is covered by the

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[1] MPEP §2164.0120

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)) *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[5] MPEP §2164.06.

[6] MPEP §2164.08

[7] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[8]

Analysis

Applicants maintain that the claimed invention is fully enabled for the following reasons.

The Office Action states that the term "an EGFR inhibitor" is allegedly broad in that it includes every inhibitor in the class of EGFR inhibitors. The PTO agrees that the specification teaches the following EGFR inhibitors: Iressa, [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A-12, cetuximab, and Tarceva. The PTO states that the genus of EGFR inhibitors is expected to be very large. For example, the post filing date art of Giaccone allegedly teaches six EGFR inhibitors (Iressa, Tarceva, Ipatinib, cenertinib, ZD6474 an AEE788) (page 8) The specification allegedly does not teach which inhibitors are associated with the changes in the level of LAMC2 or GPC3 in colon cancer (page 7, 8). Thus it is allegedly unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism. (page 8).

Applicants note that the term "EGFR inhibitor" is defined in the specification at, for example page 12, to be a molecule having the ability to inhibit a biological function of a native epidermal growth factor receptor (EGFR). After discussion with the Examiner, Applicants have amended the claims to recite the ErbB1 receptor to clarify that a specific receptor, ErbB1, is

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[8] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

meant and not the class of EGFR receptors. Support for the term ErbB1 can be found in the definition of ErbB1 from the NCI Dictionary of Cancer Terms (copy enclosed) which indicates that the EGFR receptor is also called ErbB1.

Applicants previously enclosed a declaration by Joffre, B. Baker, PhD. Dr. Baker is one of the inventors of the application. In his declaration at paragraph 6, Dr. Baker states that the patients were treated with an EGFR inhbitor selected from the group, erlotinib, gefitinib, cytoximab, EMB72000, AEE788. In paragraph 9, Dr. Baker states that all the results presented in Example 2 and Tables 3 and 4 of the application were the result of treatment with a variety of different EGFR inhibitors. Therefore it is his belief that the prognostic information obtained by overexpression of LAMC2 or GPC3 RNA transcripts or their products is applicable to treatment with the class of drugs called EGFR inhibitors which inhibit a biological function of a native EGFR.

Accordingly, Applicants have shown that the prognostic information obtained from the overexpression of LAMC2 or GPC3 RNA transcripts are applicable to any EGFR (ErbB1) inhibitor. Withdrawal of the rejection on this basis is respectfully requested.

The Office Action states that the term "corresponding gene products" is allegedly broad in that it includes every possible amino acid product which can be produced by the LAMC2 and GPC3 genes such as those that would be produced by LAMC2 and GPC3 nucleic acids having naturally and non-naturally occurring allelic, mutant and splice variants (page 5).

Without acquiescing with this rejection, Applicants have amended Claims 31, 40, 56, 57, 60 and 61 to delete the recitation of "their products" or "gene products". Applicants reserve the right to file a continuation application directed to the canceled subject matter.

Applicants maintain that the specification does show methods for the determination of the expression levels of both RNA transcripts and protein products. Applicants note that one skilled in the art would understand the meaning of RNA transcripts and their products. The specification at page 15 describes methods for the isolation of total mRNA from tumor tissues. The specification at pages 15 – 20 describes methods for the detection of RNA transcripts from the mRNA isolated from the tumor tissues. One skilled in the art would understand that such

RNA transcripts will include any native RNA transcript such as mutant and splice variants of LAMC2 and GPC3. Applicants also note that the specification at page 21, paragraphs [0063-0064] describes methods of measuring the level of proteins in tumor tissue through immunology or proteomics. One skilled in the art would understand that the RNA transcript products are native proteins present in colon tumor tissue.

Withdrawal of this part of the rejection is respectfully requested.

The Office action indicates that the specification does not teach that LAMC2 and GPC3 are overexpressed in colon cancer. The specification also allegedly does not provide an example for determining the normalized level of a representative number of corresponding gene products of LAMC2 or GPC3 in a sample.

The specification in Example 2 describes a method of extracting RNA from paraffin-embedded, formalin fixed tumor tissue from 23 patients diagnosed with colon cancer. The samples were taken from the patients prior to treatment with the EGFR inhibitor. The specification at pages 14-18 provides other methods for isolation of RNA from other types of tissue samples. The Example describes the procedure for quantitative gene expression using RT-PCR on the RNA samples. The specification at pages 14 – 18 provides other methods of analysis of the level of expression. In the example, tumor tissue was analyzed for 192 genes. The results were analyzed based on complete or partial response as one group and stable disease or progressive disease as the other group. Table 3 shows that overexpression of LAMC2 correlated with resistance to EGFR inhibitors and GPC3 had a higher mean expression value in cancer cells of patients who later did respond to EGFR inhibitor treatment than in patients that did not respond to the treatment. The second analysis grouped patients with respect to clinical benefit, where clinical benefit was defined as partial response, complete response or stable disease. Table 4 shows that GPC3 had a higher mean expression value in cancer cells of patients who later had a clinical benefit from EGFR inhibitor treatment than in patients that did not have a clinical benefit. Accordingly elevated expression of GPC3 in biopsied cancer cells is a good prognostic indicator of the outcome of treatment with an EGFR inhibitor. Tables 5A and 5B provide the accession number to the sequence for LAMC2 and GPC3 and the amplicon sequence used in the Example. Tables 6A – 6F shows the accession numbers for the forward and reverse

primers and probes used for the PCR amplification of the LAMC2 and GPC3 RNA. Accordingly one skilled in the art could readily carry out the claimed method of the invention.

It is understood by one skilled in the art that the EGF receptor (EGFR) or (ErbB1) is a dimer. Inhibitors will inhibit the action of the dimer in a number of different ways. However, if the ErbB1 dimer is inhibited then its action on the various cellular pathways downstream of the ErbB1 dimer will be inhibited. It is this action which is important in developing EGFR inhibitors for treatment of various cancers. Accordingly, the importance of the EGFR (ErbB1) inhibitor in cancer treatment is the inhibition of the EGFR (ErbB1) to act on pathways downstream. Similarly, in the present application, the prognosis is simply whether inhibition of the EGFR (ErbB1) will be effective in treatment of the cancer. Applicants have shown in the Example that the LAMC2 and GPC3 genes are prognostic indicators for the likelihood of patient response to treatment with an EGFR (ErbB1) inhibitor. Nothing further is required.

Applicants previously enclosed a declaration by Joffre, B. Baker, PhD. Dr. Baker is one of the inventors of the application. In his declaration at paragraph 6, Dr. Baker states that the patients were treated with an EGFR inhbitor selected from the group, erlotinib, gefitinib, cytoximab, EMB72000, AEE788. In paragraph 9, Dr. Baker states that all the results presented in Example 2 and Tables 3 and 4 of the application were the result of treatment with a variety of different EGFR inhibitors. Therefore it is his belief that the prognostic information obtained by overexpression of LAMC2 or GPC3 RNA transcripts or their products is applicable to treatment with the class of drugs called EGFR inhibitors which inhibit a biological function of a native EGFR.

Accordingly, one of skill in the art, given the specification, could practice the claimed invention. For these reasons, withdrawal of the rejection based on this reason is respectfully requested.

Rejection under 35 U.S.C. 112, second paragraph

Claim 51 is allegedly indefinite in the recitation of the following phrases "the lysis solution". There is allegedly insufficient antecedent basis for this limitation in the claims.

Claim 51 recites the method of claim 35, wherein RNA is isolated from colon cancer cells present in a fixed, paraffin-embedded tissue by a procedure comprising: incubating one or more sections of said fixed, paraffin-embedded tissue at a temperature of about 56 °C to 70 °C in a lysis buffer, in the presence of a protease, without prior dewaxing, to form a lysis solution; cooling the lysis solution to a temperature where the paraffin solidifies; and isolating the RNA from said cooled lysis solution.

Applicants note that there is antecedent basis for "a lysis solution" in step (a), so that reference to "the lysis solution" in step (b) and "said lysis solution" in step (c) is proper. Withdrawal of this rejection is requested.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39740-0005A**.

Respectfully submitted,

Date: July 23, 2007

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